

RESEARCH ARTICLE

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# Coronary collaterals and risk for restenosis after percutaneous coronary interventions: a meta-analysis

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## Abstract

**Background:** The benefit of the coronary collateral circulation (natural bypass network) on survival is well established. However, data derived from smaller studies indicates that coronary collaterals may increase the risk for restenosis after percutaneous coronary interventions. The purpose of this systematic review and meta-analysis of observational studies was to explore the impact of the collateral circulation on the risk for restenosis.

**Methods:** We searched the MEDLINE, EMBASE and ISI Web of Science databases (2001 to 15 July 2011). Random effects models were used to calculate summary risk ratios (RR) for restenosis. The primary endpoint was angiographic restenosis > 50%.

**Results:** A total of 7 studies enrolling 1,425 subjects were integrated in this analysis. On average across studies, the presence of a good collateralization was predictive for restenosis (risk ratio (RR) 1.40 (95% CI 1.09 to 1.80);  $P = 0.009$ ). This risk ratio was consistent in the subgroup analyses where collateralization was assessed with intracoronary pressure measurements (RR 1.37 (95% CI 1.03 to 1.83);  $P = 0.038$ ) versus visual assessment (RR 1.41 (95% CI 1.00 to 1.99);  $P = 0.049$ ). For the subgroup of patients with stable coronary artery disease (CAD), the RR for restenosis with 'good collaterals' was 1.64 (95% CI 1.14 to 2.35) compared to 'poor collaterals' ( $P = 0.008$ ). For patients with acute myocardial infarction, however, the RR for restenosis with 'good collateralization' was only 1.23 (95% CI 0.89 to 1.69);  $P = 0.212$ .

**Conclusions:** The risk of restenosis after percutaneous coronary intervention (PCI) is increased in patients with good coronary collateralization. Assessment of the coronary collateral circulation before PCI may be useful for risk stratification and for the choice of antiproliferative measures (drug-eluting stent instead bare-metal stent, cilostazol).

**Keywords:** coronary collateral circulation, meta-analysis, restenosis, therapy failure

## Background

Coronary collaterals are present in normal and diseased hearts. This coronary collateral circulation (CCC) has the potential to alleviate myocardial ischemia [1,2]. There is strong evidence that the CCC has a positive impact on survival [3,4]. However, some data suggested an increased risk for restenosis following percutaneous coronary intervention (PCI) in patients with good

collateralization; however, the findings derive from small studies and have been rather inconsistent [5,6]. The purpose of this systematic review and meta-analysis was to integrate all available data in order to provide a clearer understanding of the impact of the coronary collateral on the risk for restenosis following PCI.

## Methods

The study was performed according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analyses of observational data (Additional file 1) [7]. Planning and study design was performed by two authors (CS, PM) including creation of an

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electronic database with variables of interest (Microsoft Excel; Microsoft, Redmond, WA, USA). Primary and secondary endpoints, variables of interest and search strategy (databases, sources for unpublished data) were defined in a strategy outline that can be obtained from the study authors on request.

### Search strategy

We searched the EMBASE, PubMed, MEDLINE, BIOS, International Pharmaceutical Abstracts database, and ISI Web of Science databases from 1980 to 15 July 2011. In addition, abstract lists and conference proceedings from the 2006 to 2010 scientific meetings of the American College of Cardiology, the European Society of Cardiology, the symposium on Transcatheter Cardiovascular Therapeutics, the American Heart Association, and the World Congress of Cardiology were searched. We also considered published review articles, editorials, and internet-based sources of information <http://www.tctmd.com>, <http://www.theheart.org>, <http://www.europacronline.com>, <http://www.cardiosource.com>, and <http://www.crtonline.com> to assess potential information on studies of interest. Reference lists of selected articles were reviewed for other potentially relevant citations. No language restriction was applied. Authors of selected studies were contacted to obtain further information if needed. All prospective studies reporting on an association between restenosis probability and coronary collateral circulation were included in this analysis. Retrospective case-control studies were not considered. We focused on prospective cohort studies because our objective was to define the value of collaterals as a marker for future restenosis. Furthermore, we excluded retrospective case-control studies because we think that matching of cases with controls could introduce critical bias; and in many cases, collaterals cannot be assessed accurately in retrospect.

The detailed search syntax used for the Medline database is shown in Additional file 2. The syntax for other databases was similar, but was adapted where necessary.

### Study selection

In a two-step selection process, the titles and abstracts of all citations were reviewed by two researchers (PM, CS) to identify potentially relevant studies. In a second step, the full text of corresponding publications was reviewed to assess whether the studies met the following inclusion criteria: association of restenosis risk and the degree of coronary collateralization (Figure 1).

### Data extraction and quality assessment

Relevant information from the articles including baseline clinical characteristics of the study population and outcome measures was extracted using the prepared standardized extraction database (Excel). The quality of each

study was assessed with the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses (Table 1) [8]. Based on this scale, an additional sensitivity analysis of studies with superior quality was performed (at least seven of eight points). We did not use the quality scores for study weighting due to the limitations inherent to such an approach [9].

### Endpoints

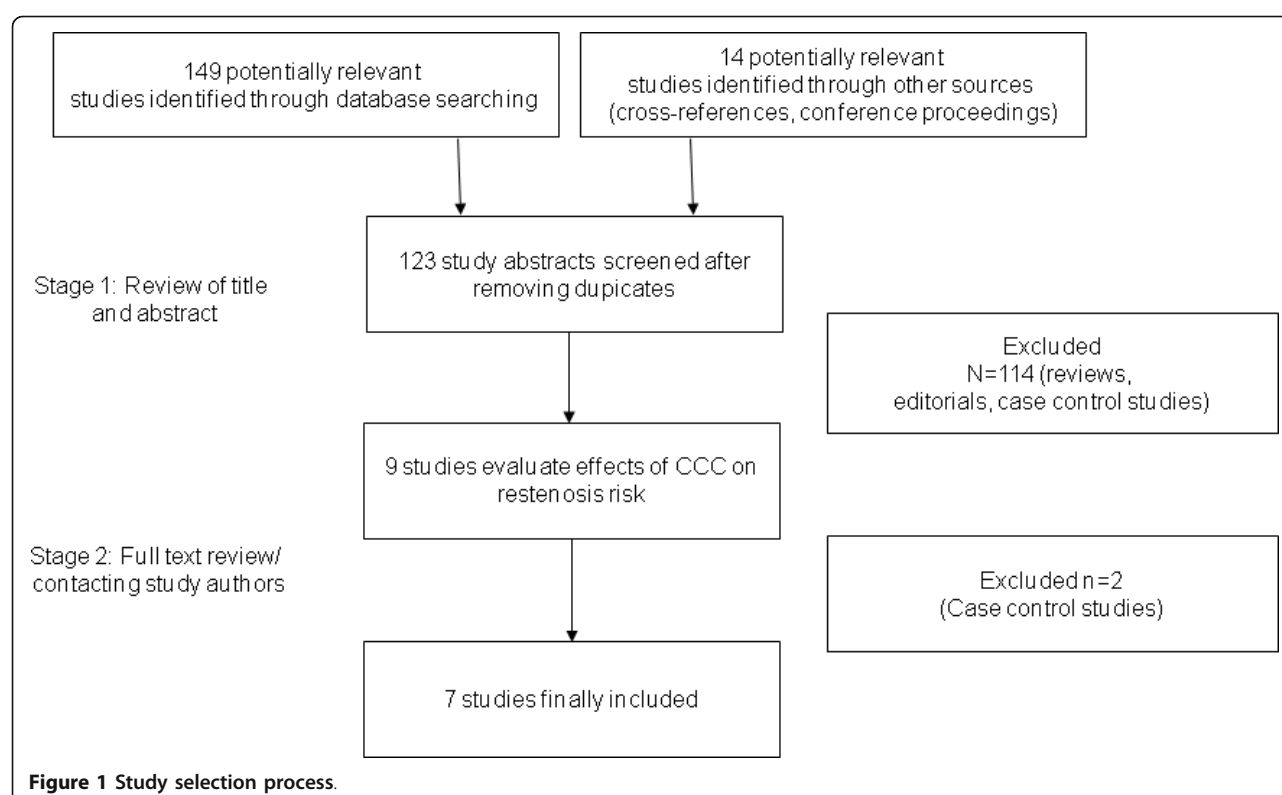
The primary endpoint of this analysis was angiographic binary restenosis (> 50% restenosis). This dichotomized endpoint definition was selected because we expected that most studies report on dichotomized values; classically, a 50% cut off has been used in angioplasty studies. This value was mainly based on the experimental work of Gould *et al.*, demonstrating blunting of the hyperemic response at a stenosis degree of 50% [10].

### Definitions

Good collateralization was defined differently for the individual studies. Three studies performed a visual assessment (Rentrop score) [11] and used a score of  $\leq 1$  for poor collateralization (no or only faintly visible collaterals). In brief, the Rentrop score assigns four degrees of collateralization depending on the presence and extension of the collateral filling of coronary epicardial vessels during a coronary angiogram (grade 0 = no collaterals; grade 1 = side branch filling of the recipient artery without filling of the main epicardial artery; grade 2 = partial filling of the main epicardial recipient artery; grade 3 = complete filling of the main epicardial recipient artery). Four studies based their collateral quantification on intracoronary pressure measurements (collateral flow index (CFI)) [12] (Table 2) and defined poor collateralization as a  $CFI < 0.25$ . The CFI defines the proportion of blood flow that derives from the collateral circulation in comparison to the antegrade blood flow through the main coronary artery. The CFI is measured with a pressure sensor tipped coronary guidewire, which is placed in the distal vessel. The collateral flow index calculation is based on the occlusion pressure during a 1-minute balloon inflation and the pressure proximal to the balloon occlusion (aortic pressure). The central venous pressure is subtracted from these two pressures to correct for the back pressure:  $CFI = (\text{occlusion pressure} - \text{central venous pressure}) \div (\text{systemic pressure} - \text{central venous pressure})$ .

### Data synthesis and analysis

Data from included studies were combined to estimate the pooled impact (risk ratio (RR)) of good collateralization versus poor collateralization. Calculations were based on a DerSimonian and Laird random-effects model [13]. This model assumes that the true effects vary between studies for unknown reasons. The primary summary measure



usually reported was the estimated average effect across studies [14]. Continuity correction was used when no event occurred in one group to allow calculation of a RR [15]. Heterogeneity among trials was quantified with the Higgins and Thompson  $I^2$  [16].  $I^2$  can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error. An  $I^2 > 50\%$  was considered as an at least moderate heterogeneity. We present as our primary results estimates of the average effect across studies with 95% confidence intervals in brackets. In addition, we also calculated 95% prediction intervals as described by Higgins *et al.* [14]. These intervals predict the effect that we would potentially expect to see in a new study. These data are presented in the Sensitivity analysis section. To assess the effect of moderator variables (study setting, method of collateral assessment, proportion of

stent use, risk of restenosis in the control groups), a mixed-effects model was used (meta-regression). For binary moderator variables, we also present the ratio of risk ratios, which was calculated with the exponential function  $\exp$  (estimated regression coefficient), with the according 95% confidence intervals. Prespecified subgroup analyses were 'setting' (elective PCI versus acute myocardial infarction (MI)) and 'collateral assessment method' (visual versus CFI). The remainder of the subgroup/meta-regression analyses were performed post hoc in an exploratory fashion.

To assess the effect of individual studies on the summary estimate of effect, we performed an influence analysis using a jackknife procedure; pooled estimates were recalculated by omitting one study at a time. We assessed publication bias visually (funnel plot) and by

**Table 1 Quality assessment of studies according to the Newcastle-Ottawa Scale**

| Lead author | Representativeness | Control group | Ascertainment | Endpoint not present at start | Assessment of outcome | Follow-up duration | Adequacy follow-up |
|-------------|--------------------|---------------|---------------|-------------------------------|-----------------------|--------------------|--------------------|
| Probst      | *                  | *             |               | *                             |                       | *                  | *                  |
| Nakae       | *                  | *             |               | *                             |                       | *                  | *                  |
| Wahl        | *                  | *             | *             | *                             | *                     | *                  | *                  |
| Perera      | *                  | *             | *             | *                             | *                     | *                  | *                  |
| Jensen      | *                  | *             | *             | *                             | *                     | *                  | *                  |
| Lee         | *                  | *             | *             | *                             | *                     | *                  | *                  |
| Antoniucci  | *                  | *             |               | *                             |                       | *                  | *                  |

**Table 2 Summary of the characteristics of the included studies**

| Lead author | Year | CCC assessment | Setting  | Follow-up (months) | PCI type  | Male (%) | Age (years) |
|-------------|------|----------------|----------|--------------------|-----------|----------|-------------|
| Probst      | 1991 | Visually       | Elective | 4 to 7             | POBA 100% | 79       | 51          |
| Nakae       | 1996 | Visually       | Acute MI | Mean 5.7           | POBA 100% | 75       | 62          |
| Wahl        | 2000 | CFI            | Elective | Mean 17            | BMS 43%   | 74       | 60.5        |
| Lee         | 2002 | CFI            | Acute MI | 6                  | BMS 74.3% | 73       | 57          |
| Antoniucci  | 2002 | Visually       | Acute MI | 6                  | BMS 64%   | 78       | 64          |
| Perera      | 2006 | CFI            | Elective | 6                  | BMS 100%  | 80       | 60          |
| Jensen      | 2007 | CFI            | Elective | 9                  | BMS 100%  | 75       | 61          |

BMS, bare metal stents; CCC, coronary collateral circulation; CFI, collateral flow index (intracoronary wedge-pressure derived collateral assessment); PCI, percutaneous coronary intervention; POBA, plain balloon angioplasty; Visually, collateral assessment with Rentrop scoring system.

formal tests (rank order correlation test and Egger's test of intercept) [17,18]. All analyses were performed with R version 2.10.1 (package 'meta') [19].

## Results

### Description of included studies

A total of 123 articles were reviewed and 7 studies including 1,425 patients satisfied the predetermined inclusion criteria (Figure 1) [5,6,20-24]. The study of Wahl *et al.* has been published as a retrospective case-control study [25]. The study focused on patients with restenosis (case) and compared them to control patients without restenosis. The data used in this meta-analysis are based on a reanalysis of the identical cohort but with dividing patients into a group with 'good collateralization' and 'poor collateralization', depending on their CFI ( $<$  threshold versus  $\geq 0.25$ ), the incidence of restenosis ( $\geq 50\%$  diameter stenosis) was calculated for the two groups (unpublished results). Table 2 summarizes the characteristics of the included studies. All patients had routine angiographic follow-up.

### Restenosis risk

Patients with a good collateralization showed a significantly increased risk for restenosis compared to patients with poor collateralization (RR 1.40 (95% CI 1.09 to 1.80);  $P = 0.009$  (heterogeneity:  $\tau^2 = 0.055$ ;  $I^2 = 52.2\%$  (95% CI 0% to 79.7%);  $P = 0.051$ ) (Figure 2).

### Investigation of heterogeneity

Analyses stratified by the method of collateral assessment showed very consistent results: good collaterals were associated with an increased restenosis risk. For visually assessed collateral assessment (based on Rentrop scoring) the RR was 1.41 ((95% CI 1.00 to 1.99);  $P = 0.049$  (heterogeneity:  $\tau^2 = 0.059$ ;  $I^2 = 64.1\%$ ,  $P = 0.062$ )) and for CFI-based collateral assessment, the corresponding RR was 1.37 ((95% CI 1.03 to 1.83);  $P = 0.038$  (heterogeneity:  $\tau^2 = 0.112$ ;  $I^2 = 56.1\%$ ,  $P = 0.077$ )) (Figure 3). There was no significant impact of the assessment method on the risk ratio in the

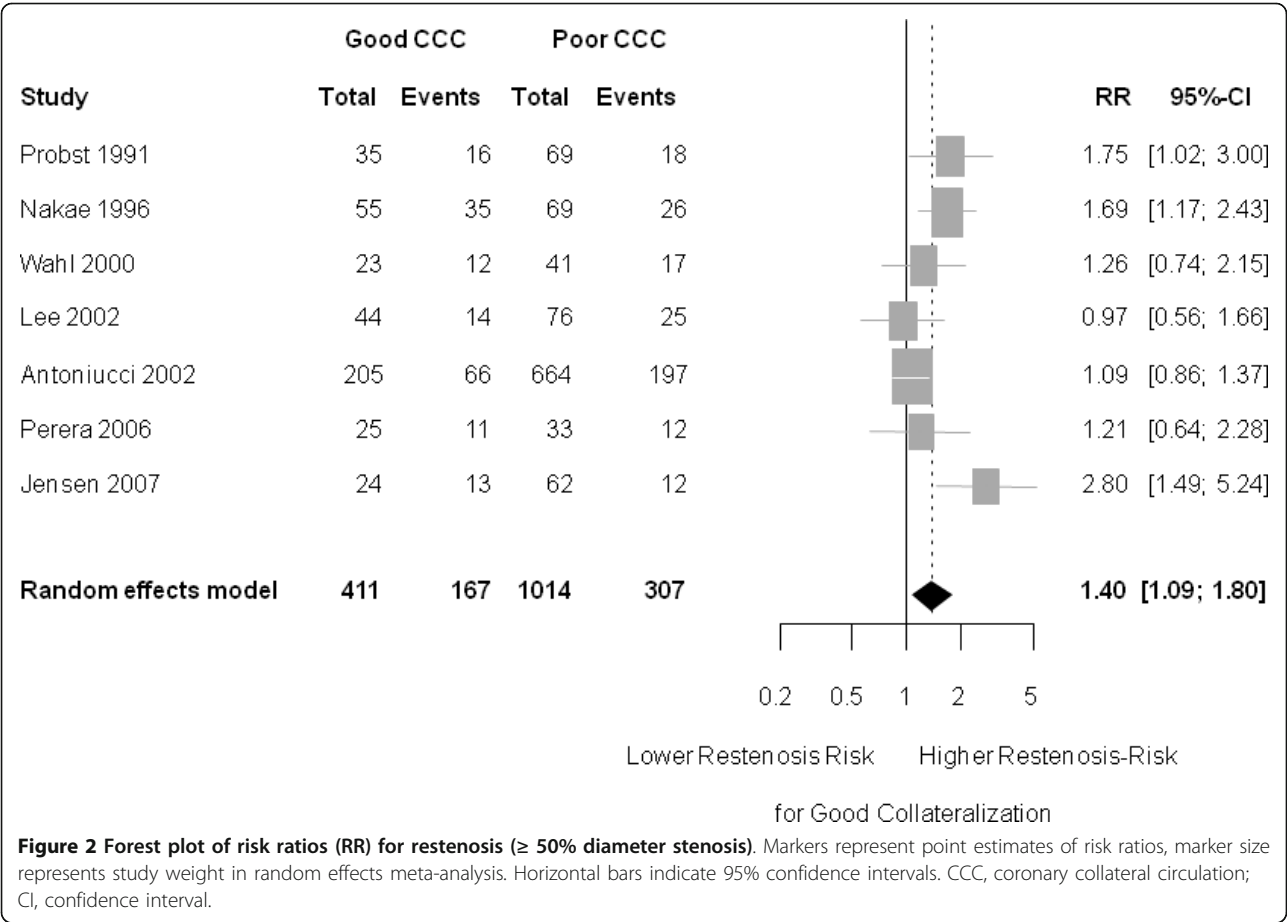
according meta-regression analysis, the ratio of risk ratio between 'visual assessment' and 'CFI based assessment' was 1.02 (95% CI 0.59 to 1.71),  $P = 0.953$ .

The results were also very consistent between the two studies using plain balloon angioplasty (POBA) in all patients and those two studies using bare metal stents (BMS) (Table 2). The proportion of BMS used in the individual studies had no significant effect on the result neither (meta-regression: slope -0.15 (95% CI -10.83 to 0.54);  $P = 0.221$ ; the meta-regression slope describes the impact of the proportion of BMS use on the study effect size; the log RR decreases on average by -0.15 when all the patients have a BMS implanted compared to the situation where none of the patients receives a BMS. (Additional file 3) Further, no significant effect of the restenosis risk in the control group (patients with poor collaterals) on the results was found neither (meta-regression: slope -2.44 (95% CI -6.54 to 1.66)  $P = 0.425$ ); this means that the log RR decreases on average by -2.44 if the restenosis risk in the control group (poor collaterals) is 100% compared to the situation where the restenosis risk is 0% (Additional file 4).

However, patients undergoing elective PCI for stable coronary artery disease (CAD) tended to show a more pronounced influence of collaterals on the restenosis risk. The risk ratio for those with good collateralization was 1.64 (95% CI 1.14 to 2.35);  $P = 0.008$  (heterogeneity:  $\tau^2 = 0.049$ ;  $I^2 = 35.9\%$ ,  $P = 0.197$ )). For patients with acute myocardial infarction, however, the respective RR was 1.23 (95% CI 0.89 to 1.69);  $P = 0.212$  (heterogeneity:  $\tau^2 = 0.049$ ;  $I^2 = 58.3\%$ ,  $P = 0.091$ )) (Figure 4). However, the according meta-regression analysis showed no statistically significant effect of this variable on the RR, the ratio of risk ratio between 'elective PCI' and 'acute MI' was 1.33 (95% CI 0.82 to 2.16),  $P = 0.243$ .

### Sensitivity analyses

None of the studies influenced the results to the extent that the conclusion would have changed; the jackknife procedure-based sensitivity analysis omitting one study at a time consistently showed that good collateralization



is associated with an increased restenosis risk (Figure 5). Specifically, excluding the only unpublished data included in this analysis (based on Wahl *et al.* [25]) did not change the overall RR estimate (RR 1.43 (95% CI 1.07 to 1.91);  $P = 0.016$  (heterogeneity:  $\tau^2 = 0.074$ ;  $I^2 = 60.1\%$ ,  $P = 0.028$ )). When considering studies with highest quality only (based on the Newcastle-Ottawa Scale; at least seven of eight points), the estimate for RR for restenosis for the group with good collaterals was very consistent but did not reach statistical significance (1.47 (95% CI 0.78 to 2.76);  $P = 0.235$  (heterogeneity:  $\tau^2 < 0.001$ ;  $I^2 = 0\%$ ,  $P = 0.866$ )); three studies were considered in this analysis [5,6,24].

The funnel plot was symmetrical (Figure 6) and formal testing did not indicate a relevant ‘small study effect’ or publication bias (Egger’s test  $P = 0.362$ , rank correlation test  $P = 0.273$ ).

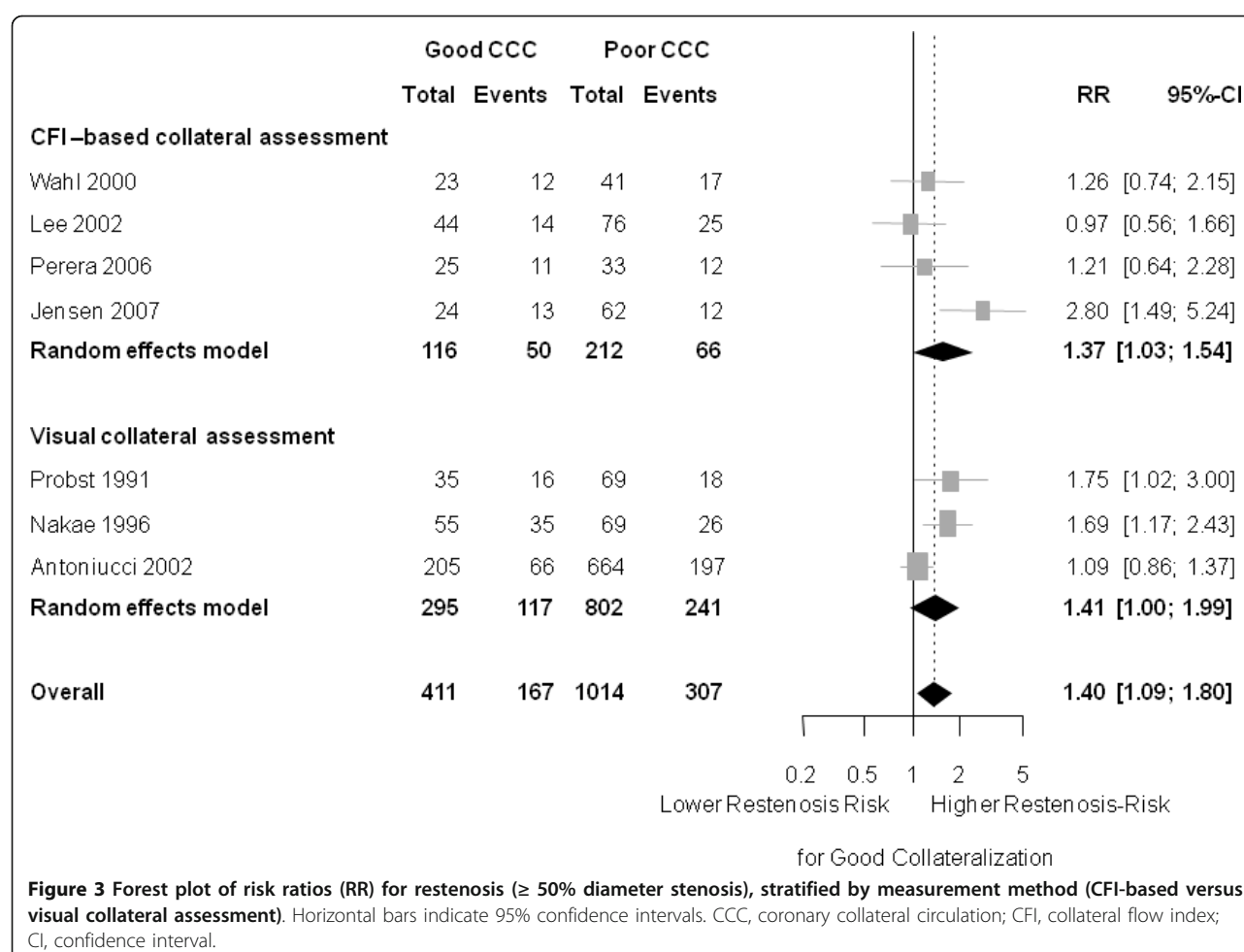
Three studies enrolled patients with acute MI. While the visual assessment of collaterals should not be altered and may even be more accurate, because the vessel of interest is occluded and avoids ‘competitive’ flow via the native and the collateral vessels, the accuracy of quantitative CFI measurements have been questioned in this

setting [26]. When excluding the one study using CFI measurements in acute MI [6], the overall result increases minimally, from RR 1.40 (95% CI 1.09 to 1.80) to RR 1.48 (95% CI 1.12 to 1.94);  $P = 0.005$  (heterogeneity:  $\tau^2 = 0.061$ ;  $I^2 = 55.5\%$ ,  $P = 0.047$ ). For the subgroup of acute MI patients, the RR increases from 1.23 (95% CI 0.89 to 1.69) to RR 1.32 (95% CI 0.86 to 2.04);  $P = 0.204$  (heterogeneity:  $\tau^2 = 0.075$ ;  $I^2 = 75.7\%$ ,  $P = 0.043$ ).

Lastly, we also calculated prediction intervals, which are wider compared to confidence intervals. For the overall results, including all studies, the RR was 1.40 with a prediction interval of 0.70 to 2.78. For the patients with elective PCI, it was 1.64 (0.47 to 5.65), for those with acute MI it was 1.23 (0.04 to 38.11).

This means that we predict that the true effect in a new study (assumed to be ‘similar’ to those studies included in the meta-analysis) would lie between RR = 0.70 and RR = 2.78 with 95% confidence. As such, although the average effect across studies of a 40% increase in restenosis in patients with a good collateralization is statistically significant, due to unexplained heterogeneity between existing results we cannot be sure of an effect in a new study.





## Discussion

This meta-analysis of seven studies shows that a 'good collateralization' is predictive for restenosis in patients undergoing PCI. This risk was found to be increased by 40% (95% CI 0% to 80%) compared to patients with poor collateralization. This association was found to be stronger in patients with stable coronary artery disease (risk increased by 64% (14% to 135%)) while it was weaker for patients with acute MI (risk increased by 23% (-11% to 69%)) and did not reach statistical significance in this subset. It has to be considered that the differences of the RR estimates between these subgroup analyses were not statistically significant. Moreover, all these values are estimates of the average effect across the different studies.

This data indicate that the degree of collateralization may be a useful and simple tool to inform individual clinical decision making, patients at high risk for restenosis may profit from the more expensive drug-eluting stents and from cilostazol, which both reduce the restenosis risk [27,28].

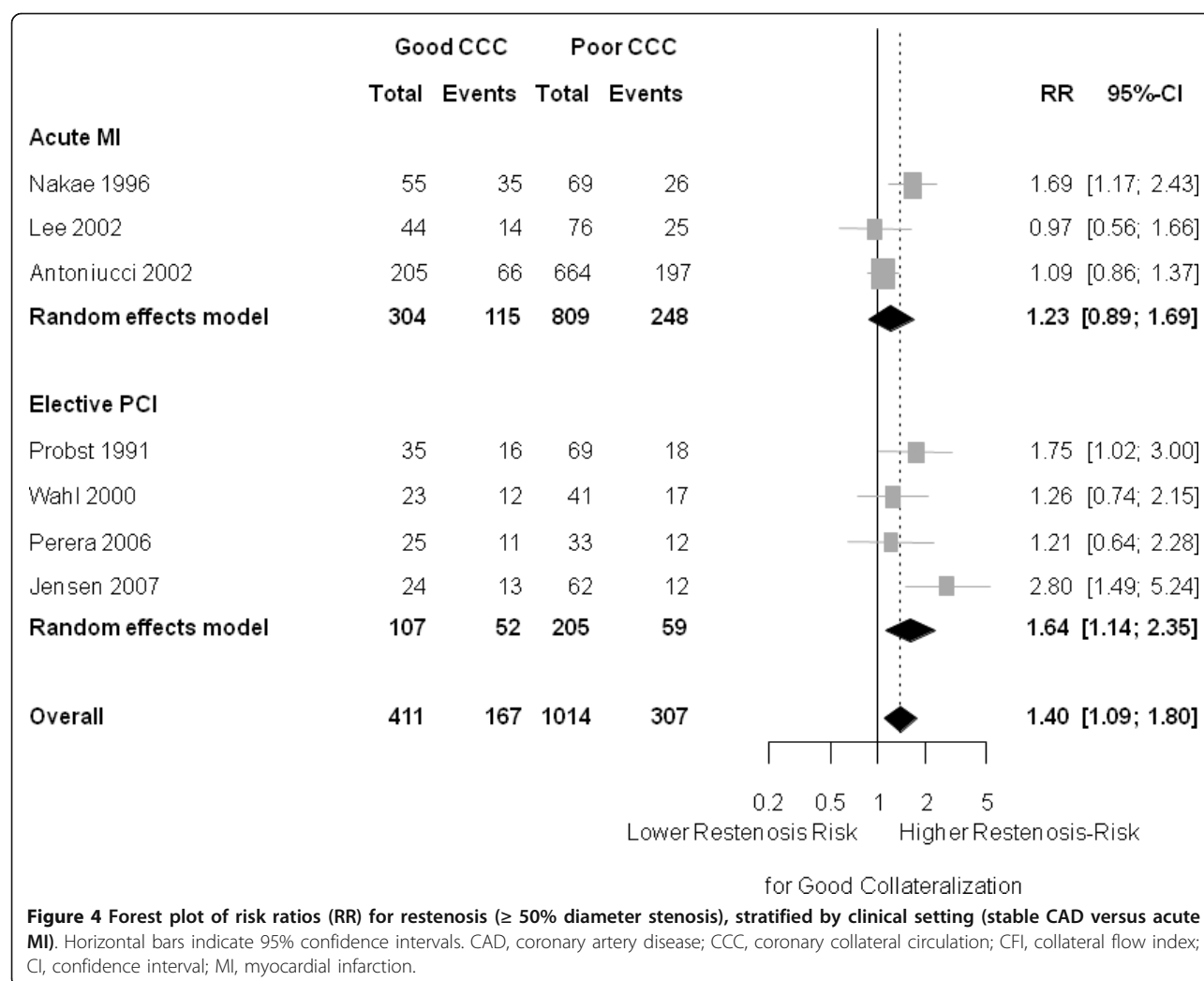
## Collaterals: good or bad?

Good coronary collateralization has been found to be associated with improved survival [3,4,29]. In this regard it may seem contradictory that good collateralization is a risk factor for restenosis after PCI. Similarly, accelerated disease progression of the native vessel after coronary artery bypass grafting (CABG) is a frequent phenomenon that does not affect the clinical benefit of CABG [30].

Coronary collaterals may be regarded as an analog to CABG in that both provide an alternative blood supply to the myocardium. Therefore, increased restenosis after PCI and improved survival benefit in patients with good collateralization are not mutually exclusive. Restenosis is usually a slow process and rarely results in a life-threatening event. This is demonstrated by the fact that most treatments that reduce the risk for restenosis, for example, drug eluting stents, do not result in improved survival.

## Potential mechanisms

One of the possible reasons for the increased risk of restenosis in case of a good collateralization is the flow

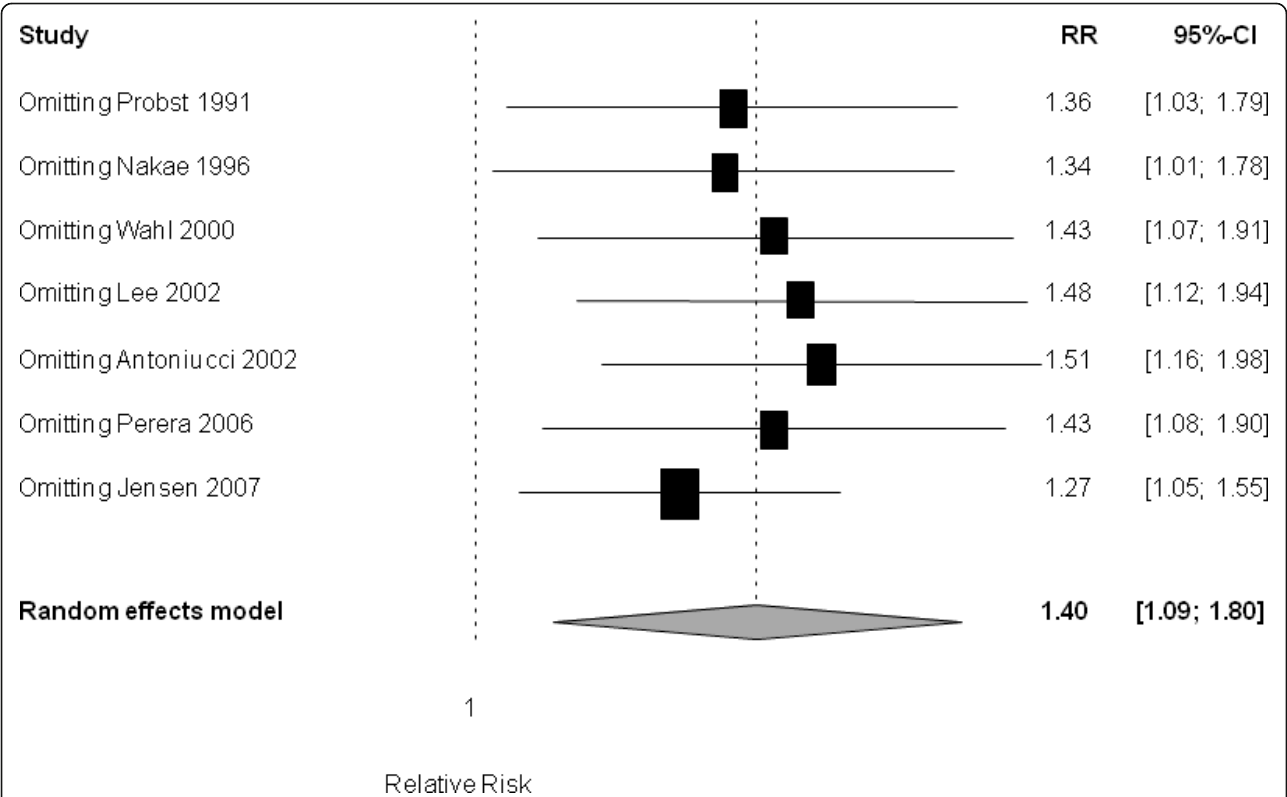


via the collaterals, which competes with the antegrade blood flow through the native vessel [23,31,32]. As mentioned above, a similar phenomenon is frequently observed in native coronary arteries in proximity to a bypass graft, which also represents a collateral circulation, leading to decreased flow through the native vessel [31,32]. This reduced flow subsequently results in a decreased shear stress on the endothelial cell layer. This shear stress is known to be atheroprotective [33]. Monocytes and platelets are key players in the pathogenesis of intimal hyperplasia and atherosclerosis; low flow and low shear stress increases the chance of cell adhesion to the vessel walls [34]. Low shear stress also modulates endothelial cell gene expression into a proinflammatory state [35]. High shear stress, on the other hand, is suppressing the expression of these proinflammatory genes, specifically via the lung Kruppel-like factor (LKLf), an anti-inflammatory endothelial transcription factor [36,37]. LKLf also reduces the expression of the

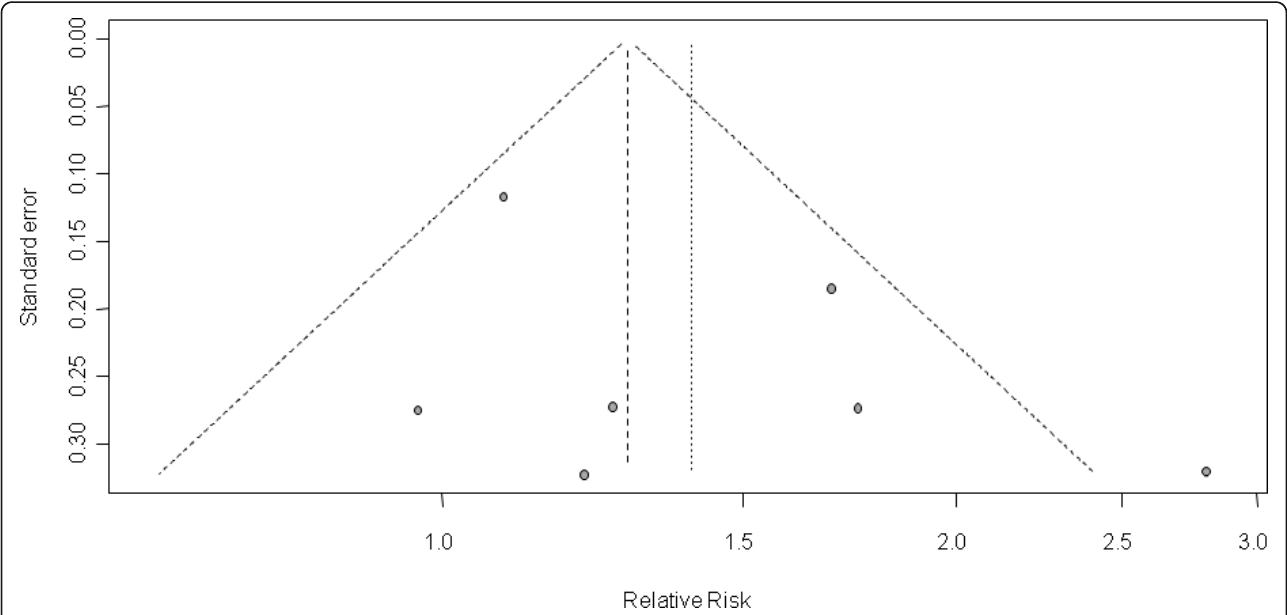
substance monocyte chemoattractant protein 1 (MCP-1). As its name suggests, MCP-1 attracts monocytes and has a proatherogenic effect [38]. However, the exact mechanism of this 'mechanotransduction', translating physical forces into changes at a molecular level, is not completely understood. Data suggest that G proteins may act as primary mechanosensors on endothelial cells; a further concept that has evolved are mechanosensitive ion channels that translate the physical force into a corresponding intracellular signal [39].

#### Coronary collaterals as a marker or as a causal risk factor for restenosis?

The major determinant of collateral function is the degree of vessel stenosis, which itself has been described to increase restenosis risk [40-42]. The studies included in this meta-analysis did not adjust for covariates such as vessel diameter stenosis or the extent of CAD. As an alternative explanation, coronary collaterals could simply



**Figure 5 Influence analysis with forest plot of risk ratios (RR) for restenosis.** Each line represents a reanalysis of the data with exclusion of one study (inclusion of six studies only) at a time to assess the influence of this particular study on the overall result.



**Figure 6 Funnel plot of the estimates of relative risk versus standard error.** Lower standard errors indicate better precision and larger study size. SE, standard error.



represent markers for more severe underlying CAD with consecutive increased risk for restenosis after PCI. This interesting question remains to be resolved in future studies. Regardless of a causal or a casual association, the degree of coronary collateralization represents a valuable and simple marker to predict the risk for restenosis.

### Outlook

Future research should evaluate possible mechanisms of this increased restenosis risk in patients with good collateralization. This patient group may show different levels of cytokine activation, inflammation, levels of reactive oxygen species (ROS) or platelet activation after percutaneous transluminal coronary angioplasty (PTCA), which may be addressed by additional pharmacologic approaches. One hypothesis to be tested is that the oxygen level distal to the vessel occlusion during angioplasty varies with varying collateralization and may lead to different ROS levels. Higher ROS levels may damage endothelial cells downstream and thereby increase the risk for restenosis.

### Limitations of this meta-analysis

Most studies used exclusively binary data for their analysis. The extent of variable of interest, collateralization, was dichotomized into 'good collateralization' and 'poor collateralization', while in fact the degree of collateralization is a continuous variable. Besides this variable of interest, the outcome was also dichotomized in most studies, using a restenosis threshold of 50%. One drawback of this approach is the impaired statistical power. Still, this meta-analysis was large enough to detect a significant influence of collaterals on restenosis risk. A related problem is the fact that all patients underwent routine angiographic follow-up. Some of the patients may have had a stable in-stent restenosis without symptoms, the routine angiographic follow-up may overrate the clinical importance of restenosis and it may overestimate the impact of collaterals on restenosis [43].

Further, the included studies did not adjust for potential confounding factors such as the severity of CAD, the diameter stenosis, and so on. Since this is a study-level and not a patient-level meta-analysis, we were not able to include these factors in our analyses. However, we think that significant confounding regarding our primary outcomes is rather unlikely. The main determinant of collaterals (our predictor) is the degree of the vessel diameter stenosis; the narrower the stenosis, the better the collaterals [40]. However, the degree of stenosis is not known to be a risk factor for future restenosis (primary outcome of our study).

Moreover, this study does not capture the dynamic of the coronary collaterals. The coronary collateral

function has been demonstrated to decrease over a 6-month period after PCI [44]. This dynamic may explain the non-significant results in the setting of acute MI. During an acute vessel occlusion, the collaterals undergo rapid changes; a fact, that limits the value of a single timepoint measurement. Further, the increased left ventricular end diastolic pressure during acute MI impairs the accuracy of the collateral assessment [26].

Another important limitation is the heterogeneity among the studies included in this analysis. The extent of heterogeneity reduces the robustness of our results. We therefore performed several subset analyses and meta-regression analysis, and found several aspects that contribute to this heterogeneity. The most important one is the difference in study populations. Four studies included patients with stable CAD while three studies focused on patients with acute MI (Table 2). Further, the earliest two studies used plain balloon angioplasty while the newest studies used bare metal stents in all patients [5,24]. Also, four studies used CFI-based collateral assessment while three studies used visual assessment of collaterals. Despite this heterogeneity between studies, the findings were very consistent in most of the subset and sensitivity analyses. Moreover, the accuracy of CFI measurements in the setting of acute MI has been questioned [26]. However, this only applies to one study [6] and excluding this study only minimally influenced the overall results (see 'Sensitivity analyses').

A further drawback of this study is that early studies used plain balloon angioplasty and later studies used BMS. No drug-eluting stents (DES) were used in the present studies. Whether the results of this meta-analysis can be generalized to DES remains unanswered. DES have further reduced the risk for restenosis; it is highest for POBA (32% in average), around 22% for BMS and around 16% for first-generation DES [45,46]. The predictive value of collaterals may be reduced in the context of DES. However, even with DES, restenosis is still a significant and unresolved problem. Our findings were consistent in the POBA and in the BMS group; they were not significantly influenced by the proportion of BMS use in the individual studies or by the average restenosis risk in the control groups (poor collaterals). We would therefore expect similar results for drug-eluting stents.

Another limitation of our study is that it does not provide further insights into possible causal mechanisms of our findings. Our considerations in the Discussion are thus rather hypothetical. This study, overall, is hypothesis generating rather than confirmatory.

With regard to the meta-regression analyses, it has to be considered that they have limited statistical power and a lack of statistical significance does not necessarily mean that there is no true effect.

## Conclusions

The results of this meta-analysis including 1,425 patients show that a good coronary collateralization indicates an increased risk for restenosis. The degree of coronary collateralization may be useful information for clinical decision making during PCI, such as stent choice (DES versus BMS) and use of cilostazol, and it may also impact the aggressiveness of the post-PCI management.

## Author information

PM is an interventional Cardiologist at UCLH, London and is leading the Yale-UCL Device Development Program. He has a degree in applied statistics and has several years of experience in clinical research on the coronary collateral circulation and on meta-analyses (for more information, see <http://www.drpascalmeier.com>). BP is a Cardiologist and Professor at the University of Michigan. He was among the first researchers to demonstrate the existence of collateral circulation in the heart, published in 1959. GK is an Associate Professor for Statistics at TU University, Dortmund. He has developed meta-analysis methods, such as the Hartung-Knapp method, which is implemented in advanced statistics software and has coauthored a book on statistical aspects of meta-analyses. AJL is a cardiologist and an Associate Professor at Yale University and an expert in PCI research and restenosis; she has had a leading role in many of the landmark trials in this field. CS is an interventional cardiologist and Professor at University Hospital Bern, and has long-standing experience in clinical research on coronary collateral circulation.

## Additional material

**Additional file 1: MOOSE Checklist.** The MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist is recommended to report on meta-analyses of observational studies and aims to ensure sufficient information about background, search strategy, methods, results, discussion, and conclusion.

**Additional file 2: Search strategy.** Detailed description of search strategy and search terms used for the systematic review.

**Additional file 3: Meta-regression of stent effect.** Meta-regression analysis of the proportion of bare-metal stents used versus the relative risk estimates.

**Additional file 4: Meta-regression of restenosis risk effect.** Meta-regression analysis of the restenosis risk in the control group (poor collaterals) versus the relative risk estimates.

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## Authors' contributions

PM was responsible for the conception and design, acquisition of data, analysis and interpretation of data, drafting the initial manuscript and revising it critically for important intellectual content. AI was responsible for acquisition of data, data control, interpretation of data and for revising the manuscript critically for important intellectual content. TT, SFdM, TK, and AJL were responsible for revising the manuscript critically for important intellectual content. GK was responsible for analysis and interpretation of data and for revising the manuscript critically for important intellectual content. CS was responsible for the conception and design, acquisition of data, interpretation of data, and for revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

## Competing interests

BP received consultant fees from Pfizer, Novartis, Merck, Takeda, Boehringer-Ingelheim, Bayer, Forrest Laboratories, GE Health Care, Relypsa, Nile Therapeutics, Aurasense and has stock options of Relypsa, Nile Therapeutics, Aurasense. BP received research grants from Medtronic, Novartis and Bayer. The other authors have no conflicts of interest to disclose.

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